REMARKS

The final Office Action mailed June 18, 2003, Paper No. 9, has been carefully studied. Upon entry of the present amendment, the application will contain claims 6-14, 16 and new claims 19 and 20; these claims define novel and unobvious subject matter under §§ 102 and 103 and should be allowed. Applicant respectfully requests favorable reconsideration, entry of the amendments presented above, and allowance.

To avoid prolixity, applicant will not repeat all of the remarks of the preceding Reply (which remarks are not withdrawn), but applicant does wish to again place the present invention in the context of the prior art.

Thus, Cynshi, which provides only a starting point, which describes active compounds used in the present invention and the utility of such compounds. However, applicant was faced with certain problems which are inherent in Cynshi, but are not addressed in Cynshi, namely the problems of stability of the active compounds and their absorbability when administered to a patient. No hint in given in the prior art as to how to improve stability and absorbability.

Cynshi broadly discloses various dosage forms at column 5 commencing at line 33, including "capsules" and "solutions". As regards oral administration, suspensions are

mentioned in test examples 4 and 5, i.e. suspension of the active compound in a 1% carboxymethyl cellulose solution (column 13, lines 4-50; column 14, lines 37-39).

Thus, there is nothing in Cynshi leading toward the present invention.

Applicant has solved the aforementioned problems by dissolving the active compound in soybean oil which "is especially preferred" (applicant's specification, page 5, line 23). As regards the effects produced, the final sentence of test example 1 (page 13, lines 4 and 5) states as follows:

> Relatively high stability was observed in the case where soybean oil was used.

And, with respect to increasing absorbability, please see the last sentence of test example 2 (page 14, lines 11-14):

> Sample 1 in which soybean oil was used as solvent showed the highest plasma level shift and the AUC value for sample 1 was about 4 time and about twice as high as compared with those for samples 2 and 3, respectively.

Thus, the present applicant has discovered that a soft capsule containing the active compound and soybean oil has increased stability of the active compound, and when administered results in increased absorbability.

Applicant respectfully notes that what an applicant states in his or her specification is to be accepted by the PTO in the absence of evidence or good reasoning to the contrary. From *In re Costello*, 178 USPQ 290, 92:

> There is no justification for simply ignoring appellant's allegations of unexpected results.

From *Ex parte Johnson*, 40 USPQ 576:

> The examiner makes no showing... [that applicant's statement is incorrect] and this tribunal is not so expert in the art as to disagree with applicant's sworn description and agree with the examiner without cause.

From *In re Andrews*, 168 USPQ 360, 66:

> We cannot take judicial notice of... the impossibility of what appellant asserts... . Accordingly, we reverse the rejection which, in our view, ignored the thrust of appellant's application in this regard.

From *Ex parte Ilgen and Michl*, 172 USPQ 316, 17:

> As the main opinion notes, appellant's specification asserts an improved result... . The examiner erred in failing to show cause for not giving effect to this assertion.

From *Ex parte Leonard*, 187 USPQ 122, 123-24:

> ..., we fail to find any suggestion from the collective teachings before us that... the combination... as claimed... [would have the results alleged]. This is a totally new and surprising beneficial result,... . Such unexpected results must, of course, be taken fully into account,... [omitted]... .
>
> We should note that in so holding..., we rely heavily on appellant's representations... . We are aware of no good reason to challenge appellant's presumptively accurate disclosure... .

The prior art provides **NO** evidence or good reasoning contrary to what is stated in applicant's specification.

Applicant believes that the final rejection is unjustified, and that the claims as previously pending define novel and unobvious subject matter and should have been allowed. Nevertheless, upon entry of the amendments presented above, the claims will be limited to the situation where the dihydrobenzofuran derivative is only a single compound, namely 4,6-di-tert-butyl-2,2-di-n-pentyl-5-hydroxy-2,3-dihydro-benzofuran, hereinafter referred to as "BO-653".

No new issues are raised by the amendments presented above, because claim 19 is precisely of the scope of previous claim 2, and claim 20 is of precisely the same scope as previous claim 18, further limited according to claim 2. The above amendments are proposed without prejudice to applicant's rights, applicant reserving the right to pursue broader claims in a continuing application if applicant chooses to do so, without any penalty whatsoever, such rights including those provided by §§ 120 and 119.

Claims 1, 2, 6-14, 16 and 18 have been again rejected under §103 as obvious from Borkan in view of Cynshi. This rejection is again respectfully traversed.

As noted above, new claims 19 and 20 are proposed above to replace claims 1, 2 and 18, and are limited to BO-653. As is clear from applicant's specification, BO-653 is liable to

be oxidized while being stored as a solution. Further, BO-653 has a low capability of being absorbed by the body due to its poor water-solubility.

According to the present invention, however, inhibition of the oxidization and improvement in the absorption of BO-653 have been achieved by dissolving the compound in soybean oil and filling the solution into a soft capsule. The oxidization-inhibiting and absorption-improving activities of soybean oil are shown in the examples of applicant's specification only on BO-653 due to the liability to be oxidized and the poor water-solubility of this compound.

Although the excellence of the absorption-improving activity of soybean oil is confirmed by reviewing the pharmacokinetic parameters shown in Table 6 of the present specification, it can also be confirmed by a statistical analysis using Dunnett's t-test for the original data which were used for determining pharmacokinetic parameters but not shown in the specification as filed. The original data are shown in Attachment A.

Using the data for Sample 1 as a control, which sample is a BO-653 solution in soybean oil shown in Table 4, a statistical analysis was conducted and the following P values were obtained:

$P<0.05$ for C_{max} of Sample 2 (a BO-653 solution in MCT);
$P<0.05$ for C_{max} of Sample 3 (a BO-653 solution in aqueous gum arabic);
$P<0.01$ for AUC_{0-48h} of Sample 2; and
$P<0.05$ for AUC_{0-48h} of Sample 3.

These P values are sufficient to statistically confirm the excellence of the absorption-improving activity of soybean oil in BO-653. This proves unobvious subject matter.

In contrast, Borkan suggest neither the oxidation-inhibiting nor absorption-improving activity of soybean oil. This is because there is no need for the inhibition of the oxidation or improvement of the absorption of the biologically-active compounds discussed in Borkan because the Borkan compounds are not liable to be oxidized and are not poorly water soluble. In fact, the biologically-active compounds used in the Examples of Borkan such as ascorbic acid are not liable to be oxidized and are highly water-soluble.

One of ordinary skill in the art would not have been motivated to select soybean oil from the non-toxic liquid bases disclosed in Borkan and to select BO-653 from the numerous compounds disclosed in Cynshi and to combine them to obtain the claimed seamed soft capsule formulation, because it would not have been expected that the combination would allow the inhibition of the oxidation and the improvement of the absorption of BO-653.

Withdrawal of the rejection is respectfully requested.

Replying further to the "Response To Arguments" section of the Final Action, applicant respectfully points out that the data of applicant's specification are indeed statistically significant as pointed out above and in Attachment A. Moreover, the claims are now proposed to be limited to BO-653 consistent with previous claim 2. Applicant respectfully invites attention to legal precedent which holds that improved results can be proven by examples in an applicant's specification, including *Ex parte Drewe*, 203 USPQ 1127, 1128; *In re Margolis*, 228 USPQ 940; *In re Robins*, 166 USPQ 552, 558; and *In re Kohler*, 177 USPQ 399, 400.

The fact of the matter is that the applicant faced a problem not faced or recognized by either reference. Applicant recognized this problem, and applicant sought and successfully obtained a solution to this problem. All this constitutes non-obvious subject matter, i.e. subject matter for which there is not the remotest suggestion in the prior art. With respect, it cannot be fairly or reasonably denied that there would have been no reasonable expectation of applicant's results provided by the prior art, particularly in view of the fact that such

art provides no evidence of even the recognition of the problem, let alone its solution.

Applicant respectfully requests withdrawal of the rejection.

Claims 1, 2, 6-14 and 16 have been rejected under §103 as obvious from Borkan in view of Cynshi and further in view of DeMichele. This rejection is again respectfully traversed.

Applicant respectfully repeats by reference the arguments against this rejection appearing in the last Reply, commencing at page 11 and extending through the top of page 13.

DeMichele does not make up for the deficiencies of the proposed combination of Borkan in view of Cynshi as discussed above and previously. Therefore, even if the combination were obvious to the person of ordinary skill in the art at the time the present invention was made, such combination would not reach applicant's invention for the reasons pointed out above with respect to the rejection based solely on the proposed combination of Borkan in view of Cynshi. No *prima facie* case of obviousness exists, and in any event applicant has proven the presence of unobvious results.

Applicant respectfully requests withdrawal of the rejection.

Favorable reconsideration, entry of the amendments presented above and formal allowance are respectfully requested.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By _____
Sheridan Neimark
Registration No. 20,520

SN:ma
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YUAS\Katsuki1\PTO\AMD 18Nov03.doc

ATTACHMENT A

SAMPLE 1	Cmax (µg/mL)	AUC_{0-48h} (µg h/mL)
1	4.3	37.4
2	5.6	41.5
3	3.3	32.2
4	11.1	67.5
Mean ± SD	**6.1 ± 3.5**	**44.6 ± 15.7**

SAMPLE 2	Cmax (µg/mL)	AUC_{0-48h} (µg h/mL)
1	1.8	11.2
2	1.6	9.4
3	2.6	16.1
4	2.5	5.7
Mean ± SD	**2.1 ± 0.5**	**10.6 ± 4.3**

SAMPLE 3	Cmax (µg/mL)	AUC_{0-48h} (µg h/mL)
1	2.3	27.1
2	1.0	15.3
3	2.2	19.1
4	2.7	31.4
Mean ± SD	**2.2 ± 0.3**	**23.2 ± 7.3**